REMARKS

Introductory Comments

Claims 45-48 and 63-65 were examined in the Office Action under reply and rejected solely under 35 U.S.C. §103(a). This rejection is traversed for reasons discussed below.

Applicants note with appreciation the withdrawal of the previous rejections under 35 U.S.C. §103(a) over (1) Cho et al., *Vaccine* (1999) 17:1136-1144 in view of Lagging et al., *J. Virol.* (1995) 69:5859-5863 or Geissler et al., *J. Immunol.* (1997) 159:5107-5113; and (2) International Patent Publication No. WO 91/15771 to Houghton et al.

Priority

The Office maintains the present application is not entitled to the benefit of priority of U.S. Provisional Application Serial No. 60/161,713, filed October 27, 1999. The Office argues applicants did "not assert the objection" in the previous response. However, this statement is inaccurate. Applicants indeed dispute the Examiner's position on page 4 of the previous response.

Additionally, the Examiner argues against priority stating the Rule 131 Declaration submitted with the previous response shows applicants had possession of a construct encoding a fusion protein containing NS3, NS4 and NS5 prior to March 1999 but the protein does not include the core antigen. However, the Declaration is irrelevant to the question of priority. In particular, the Declaration is submitted to overcome a reference dated March 1999, seven months prior to October 27, 1999, the priority date of the present application.

Moreover, as previously explained to the Office, the '713 application includes descriptions in the specification that evidence applicants' invention encompasses fusions as claimed. The Office's attention is directed to pages 4-5, bridging paragraph (emphasis added):

> The genomes of HCV strains contain a single open reading frame of approximately 9,000 to 12,000 nucleotides, which is transcribed into a polyprotein. An HCV polyprotein is cleaved to produce at least ten distinct products, in the order of NH2- **Core**-E1-E2-p7-NS2-NS3-NS4a-NS4b-NS5a-NS5b-COOH. Fusion proteins of the invention (NS3NS4NS5a fusion proteins) **comprise** HCV NS3, NS4 (NS4a and NS4b), and NS5a polypeptides

> (NS3NS4NS5a fusion proteins) or **comprise** HCV NS3, NS4 (NS4a and NS4b), NS5a, and NS5b polypeptides (NS3NS4NS5aNS5b fusion proteins).

The '713 application further explains at page 8, lines 15-23 (emphasis added):

> Polynucleotides contain **less than an entire HCV genome** and can be RNA or single- or double-stranded DNA. Preferably, the polynucleotides are isolated free of other components, such as proteins and lipids. NS3NS4NS5a polynucleotides encode the NS3NS4NS5a fusion proteins described above, and thus **comprise** coding sequences for NS3, NS4, and NS5a polypeptides. NS3NS4NS5aNS5b polynucleotides encode the NS3NS4NS5aNS5b fusion proteins described above, and thus **comprise** coding sequences for NS3, NS4, NS5a, and NS5b polypeptides. Polynucleotides of the invention **can also comprise other nucleotide sequences**, such as sequences coding for linkers, signal sequences, or ligands useful in protein purification such as glutathione-S-transferase and staphylococcal protein A.

These passages, when read in concert, would certainly be understood by one of skill in the art to cover fusions including other proteins, such as fusions including additional regions from HCV.

In particular, the first passage above explains that the core region is one of the products cleaved from the polyprotein, along with the NS3, NS4 and NS5 regions. Moreover, both the first and second passages above make clear that the fusions "comprise" NS3, NS4 and NS5 proteins. Because the term "comprise" is open-ended, the '713 application expressly contemplates that other proteins will be present. Further, the second passage quoted above explicitly states that the polynucleotides contain **less than an entire HCV genome.** Implicit in this statement is that the polynucleotides can include other regions from the HCV genome, so long as the entire genome is not present. This statement, coupled with the explanation that the core region is part of the polyprotein encoded by the genome, makes clear that the inventors contemplated the presence of the core region in the fusions. Finally, the last sentence of the second passage quoted above states polynucleotides of the invention **can also comprise other nucleotide sequences**. When these passages of the application are read together, it is clear that a fusion including core in addition to NS3, NS4 and NS5, was indeed intended.

Accordingly, applicants continue to assert they are in fact entitled to the benefit of the '713 application.

Overview of the Above Amendments

Claims 45 and 63-65 have been cancelled herein. Claim 46 has been amended to incorporate recitations from claims 45 and 64.

Amendment and cancellation of the claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicant expressly reserves the right to file one or more continuing applications hereof containing the canceled or unamended claims.

35 U.S.C. § 103

Claims 45-48 and 63-65 continue to be rejected under 35 U.S.C. § 103(a) as being unpatentable over Houghton et al. (U.S. Patent No. 5,683,864; hereinafter "Houghton '864") or Houghton et al. (U.S. Patent No. 6,312,889; hereinafter "Houghton '889"). Initially, applicants note Houghton '889 is a continuation application of Houghton '864. Accordingly, the disclosure in the two patents is the same and the following arguments are equally applicable to both references.

All of applicants' present claims relate to compositions comprising a polynucleotide encoding an immunogenic fusion protein, a pharmaceutically acceptable excipient and an adjuvant. The Office argues "an adjuvant addition in an immunogenic composition is well known and commonly used" by a skilled artisan to obtain a "more effective immune response." Office Action, page 3. However, this statement misses the point of the previous argument.

As previously explained, both of Houghton '864 and Houghton '889 relate to **immunoassays** using **polypeptide** antigens for detection of antibodies in sera. Neither of these references pertains to nucleic acid immunization with **polynucleotide compositions** encoding HCV antigens for eliciting an immune response, as in the instant application. There simply would be no reason to add an adjuvant to the polynucleotides described in the Houghton references as such would have no purpose in immunoassays.

Compositions effective for detection of HCV antibodies, as used in the Houghton references, are not necessarily effective for immunization against HCV. Detection of antibodies merely requires that antibodies specifically bind to an antigenic reagent, whereas eliciting an immune response is complicated by the diverse interactions among the many molecules and cells of the immune system and their complex regulation, all of which is required to effectively generate cellular and humoral immunity. Thus, problems like antigenic competition and immunodominance, which diminish the efficacy of compositions comprising antigen mixtures in immunization, may not similarly interfere with HCV detection in immunoassays. There can be no reasonable expectation of success that compositions comprising a polynucleotide encoding the particular combinations of HCV antigens, as claimed, would be effective in immunization against HCV based on the teachings of these references.

The Office has failed to provide evidence that the claimed invention is a "predictable use of prior art elements according to their established functions." *KSR Int'l Co. v. Teleflex, Inc.*, 82 USPQ2d 1385, 1396 (U.S. 2007). In fact, the evidence is to the contrary. The cited art fails to provide evidence that a skilled artisan would in fact be motivated to make a composition comprising a polynucleotide encoding the claimed HCV fusion polypeptides as claimed. One of skill in the art simply would not expect that an immunoreactive component, such as used in the Houghton immunoassays, would also be immunogenic. Thus, there would be no reason to add an adjuvant in order to enhance an immune response.

Furthermore, neither of the Houghton references describes or suggests a fusion protein comprising a full length NS3 polypeptide, as recited in the claims. On the contrary, the references describe a fusion protein comprising an NS3 region derived from residues 1050-1640 (see Houghton '864 at col. 4, lines 21-23; Houghton '889 at col.4, lines 8-10; and Houghton '771 at page 6, lines 31-33).

Thus, not only do Houghton '864 and Houghton '889 fail to disclose or suggest polynucleotide compositions as claimed, the Houghton references also fail to disclose or suggest the particularly claimed polynucleotides that are present in such compositions.

For at least these reasons, withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

In light of the above remarks, applicants submit that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, applicants invite the Examiner to contact the undersigned at 650-493-3400.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

Please direct all further written communications regarding this application to:

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Respectfully submitted,

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